Journal of Forensic and Legal Medicine 20 (2013) 962–964

Contents lists available at ScienceDirect

Journal of Forensic and Legal Medicine

journal homepage: www.elsevier.com/locate/jflm

Case report

Acute fatal poisoning with Tolfenpyrad

Wakako Hikiji, MD, PhD, Medical Examiner [a, *], Koji Yamaguchi, PhD, Assistant Professor [b], Kanju Saka, BSc, Technical Support Specialist [c], Makiko Hayashida, PhD, Associate Professor [b], Youkichi Ohno, MD, PhD, Professor [b], Tatsushige Fukunaga, MD, PhD, Director [a, 1]

[a] Tokyo Medical Examiner's Office, Tokyo Metropolitan Government, 4-21-18 Otsuka, Bunkyo-ku, Tokyo 112-0012, Japan
[b] Department of Legal Medicine, Graduate School of Medicine, Nippon Medical School, Japan
[c] Department of Forensic Medicine, Graduate School of Medicine, The University of Tokyo, Japan

ARTICLE INFO

Article history:
Received 29 September 2012
Received in revised form
11 July 2013
Accepted 20 August 2013
Available online 29 August 2013

Keywords:
Tolfenpyrad
Poisoning
Pesticide
Naphthalene

ABSTRACT

The authors present a fatal case of poisoning with Tolfenpyrad (TFP), a pesticide first approved in Japan in 2002. A man in his fifties was found dead in the supine position at his son's home and the small towel with a smell of naphthalene was found nearby. Forensic autopsy was unremarkable, except for a very small amount of light pink fluid in the stomach, with naphthalene odour. The toxicological analyses revealed the presence of TFP and its major metabolite PTCA (4-[4-[(4-chloro-3-ethyl-1-methylpyrazol-5-yl)carbonylaminomethyl]phenoxy]benzoic acid), together with naphthalene and methyl naphthalenes in the post-mortem sample, with liquid chromatography–mass spectrometry (LC–MS) and gas chromatography–mass spectrometry (GC–MS) respectively. The plasma concentrations of each substance were quantified as 1.97 μg/ml (TFP), 2.88 μg/ml (PTCA), 1.70 μg/ml (naphthalene), 0.67 μg/ml (1-methyl naphthalene) and 1.44 μg/ml (2-methyl naphthalene). According to these results together with autopsy findings, the cause of his death was determined to be acute Tolfenpyrad poisoning. This is the first case report of fatal poisoning attributable to an intake of TFP product.

1. Introduction

Tolfenpyrad (TFP) is a pesticide developed in Japan and was first approved in 2002. It possesses a pyrazole–carboxamide structure, as shown in Fig. 1. The mechanism of cytotoxicity is brought by the inhibition of Complex I in the respiratory electron-transfer chain of mitochondria, which makes it effective against the pests resistant to pre-existing insecticides with other modes of action.[1] It has been registered for commercial use in several countries other than Japan to date, including the Dominican Republic, Thailand, the United Arab Emirates, Indonesia and the United States of America.

Ten fatal TFP poisoning cases were reported in Japan between 2003 and 2010.[2,3] Another published report showed ten TFP poisoning cases in Japan up to 2009, consisting of 1 fatal and 1 non-fatal cases, with the outcome of 8 remaining cases unknown.[4] Despite these statistical data, no case report on this new pesticide has been published to date. In this paper, a fatal case of poisoning of TFP in an adult male is presented, with a literature review.

2. Case history

A man in his fifties without any significant medical history was found in the supine position at his son's home in a state of cardiac pulmonary arrest and was pronounced dead on arrival at hospital. He had no regular medication and no history of attempted suicide. There was no distinct evidence of drug intake at the scene, but the small towel beside him had a chemical smell according to his son, the first discoverer of the corpse. As the cause of death could not be ascertained at the inquest, a forensic autopsy was carried out approximately 23 h after his death. The decedent was 164 cm in height and weighed 61 kg. The external and internal examination, both gross and microscopic findings, revealed no remarkable pathomorphological changes, except for the prominent postmortem lividity. There was no distinct evidence of intake of toxicological agents, such as erosion or discolouration of upper respiratory and gastric tracts. All organs were strongly congested. The weights of lungs were 514 g left and 600 g right, both strongly

* Corresponding author. Tel.: +81 3 3944 1481; fax: +81 3 3944 7585.
E-mail address: hikiji@kyudai.jp (W. Hikiji).
[1] Tel.: +81 3 3944 1481; fax: +81 3 3944 7585.

1752-928X/$ – see front matter
http://dx.doi.org/10.1016/j.jflm.2013.08.012

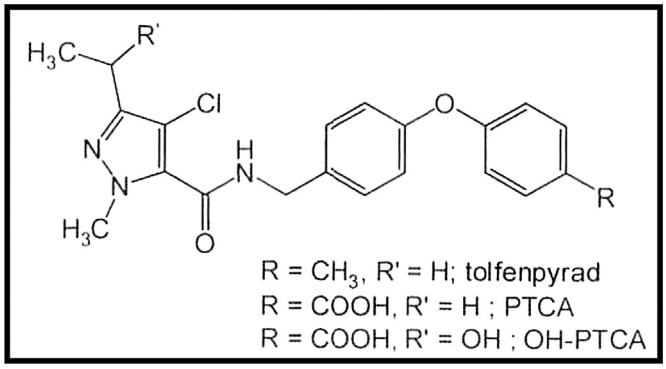

Fig. 1. Molecular structures of Tolfenpyrad (TFP), 4-[4-[(4-chloro-3-ethyl-1-methylpyrazol-5-yl)carbonylaminomethyl]phenoxy]benzoic acid (PTCA) and OH-PTCA.

oedematous. The heart was of normal size, weighing 366 g, and the coronary arteries were free of atherosclerosis. No clots were found in the heart blood. A small amount of light pink liquid material was found in the stomach, with naphthalene odour. Intracardiac blood was reserved for further toxicological analyses but a substantial amount of peripheral blood, gastric contents and urine could not be obtained. The sample was stored at 4 °C until analyses and the routine toxicological study was carried out using the gas chromatography–mass spectrometry (GC–MS).

3. Results and discussion

Although the initial drug screening for acids and bases using the intracardiac blood by GC–MS was negative, the drug profiling system detected a pronounced peak. However, a compatible drug was not registered in the drug library released in 1992 and could not be identified. Additional toxicological analyses performed at forensic laboratories in Nippon Medical School and the University of Tokyo confirmed the presence of TFP, its major metabolite PTCA (4-[4-[(4-chloro-3-ethyl-1-methylpyrazol-5-yl)carbonylaminomethyl]phenoxy]benzoic acid) as well as naphthalene and methyl naphthalenes in plasma. TFP and PTCA were both identified by retention time and mass spectrum acquired in scan mode using liquid chromatography–mass spectrometry (LC–MS), whereas GC–MS was used for the analyses of naphthalene and methyl naphthalenes. The detailed analytical methods have been described in the previously published paper.[5] Post-mortem toxicology did not reveal any other toxic substances. Table 1 shows the plasma concentration of TFP, PTCA, naphthalene, 1-methyl naphthalene and 2-methyl naphthalene in the presented case.

The number of fatal intoxications with pesticides has been declining in developed countries due to laws restricting the distribution of highly toxic chemicals.[6] Nevertheless, forensic scientists and clinicians must be aware of the fact that there are fatal cases being reported constantly worldwide and new products with significant morbidity and mortality keep being released and distributed, which include TFP.

Table 1
The plasma concentrations of Tolfenpyrad (TFP), 4-[4-[(4-chloro-3-ethyl-1-methylpyrazol-5-yl)carbonylaminomethyl]phenoxy]benzoic acid (PTCA), Naphthalene, 1-methyl naphthalene and 2-methyl naphthalene (μg/ml) detected in this case.

	TFP	PTCA	Naphthalene	1-Methyl naphthalene	2-Methyl naphthalene
Plasma concentration (μg/ml)	1.97	2.88	1.7	0.67	1.44

TFP is commercially available in form of water dispersible powder or emulsifiable concentrate (EC), and either product can be purchased without any special license or proof of ID in Japan. Both naphthalene and methyl naphthalenes are the ingredients of TFP EC product, which probably accounted for the odour of the gastric content and those detected in plasma in the presented case.

It is predicted that the unique mechanism of cytotoxicity of TFP, the inhibition of Complex I in the respiratory electron-transfer chain in mitochondria, brings rapid effects to pests, and if used inappropriately, to other organisms. The documented symptoms of TFP intoxication in humans include impaired consciousness, respiratory depression, mydriasis, blood pressure reduction, metabolic acidosis, vomiting and mucosal erosions of alimentary tracts.[4] The actual symptoms remain unknown in the presented case as the man was already in a state of cardiac pulmonary arrest when found. However, there was no evidence of vomiting or incontinence at the scene. On the other hand, the autopsy findings, such as the prominent formation of postmortem lividity and the absence of clots in cardiac blood are compatible with the characteristics of sudden death, which are in accordance with TFP intoxication.

The tabulated reference range for TFP is not well established as with other newly developed chemicals, where a sufficient number of clinical case reports is yet to be published. The only comparable study is an oral administration experiment of rats conducted by the manufacturer, although it needs an assumption that the bioavailability of TFP in rats and in humans correlates with each other. In this experiment, the radioactivity of the samples was measured and expressed in terms of TFP concentration, after ingesting ^{14}C labelled TFP to rats at a dose of 320 mg/kg, which was close to LD_{50} in male rats. The TFP concentration at 6 h after ingestion were 5.18–6.97 μg/ml (one fatal individual was excluded). The sum of the concentrations of TFP and PTCA in the presented case is of the same magnitude (4.85 μg/ml) to the results obtained from the animal experiment study. It is therefore predicted that the presented case is clearly consistent with an overdose, but furthermore, lethal intoxication.[1]

Tebufenpyrad is another pesticide with a pyrazole–carboxamide structure, and was approved and commercialized in 1993 in Japan. It is considered to bring toxicity to pests by the same mechanism of action as TFP. Although there are a number of reported poisoning cases, only 1 human lethal case report in the Japanese language can be found to date. The blood concentration of tebufenpyrad in this published case was 1.6 μg/ml.[7] It is predicted that 1.97 μg/ml, the TFP concentration in the presented case is within the lethal level, as the LD_{50} value of tebufenpyrad is reported to be higher than that of TFP based on the animal experiments.[1,4]

As previously stated, naphthalene and methyl naphthalenes were also detected in plasma of the presented case. The clinical consequences of naphthalene ingestion may include headache, vomiting, diarrhoea, abdominal pain, fever, altered mental status and a decrease in urine output, which may persist up to 48 h.[8] It has also been pointed out that oxidative stress from the hepatic metabolites of naphthalene causes haemolysis and methaemoglobinaemia.[9] It is predicted that naphthalene and their metabolites had a little toxicological relevance in relation to the cause of death of the presented case, as there were no evident morphological changes found in organs including liver or kidneys. There is a report stating that TFP plays the main role in poisonings after ingestion of the EC form of TFP, as the effects are seen very rapidly and the symptoms observed are not typical to those of naphthalene poisonings.[4] The authors therefore predicted that, on the basis of case history, external and internal autopsy findings, microscopic examination and analytical data, the death of the present case is attributable to an acute TFP poisoning.

Apart from TFP and tebufenpyrad, pesticides such as fenazaquin, fenpyroximate, pyridaben, pyrimidifen and rotenone are also believed to bring toxicity by the inhibition of Complex I in the respiratory electron-transfer chain in mitochondria.[10] There are a number of experimental reports on these chemicals but only 1 fatal case report on pyrimidifen and 3 on rotenone can be found on human poisoning in the English literature out of those mentioned above.[11–14] The abuse potential and forensic importance of these substances are also in need to be established.

The presented case is the first reported fatal poisoning attributable to TFP. Forensic autopsy with detailed toxicological studies were essential to clarify the cause of death, as there were a very few hints of TFP ingestion at the point of inquest. However, whether a family member of the deceased attempted to conceal the evidence of TFP ingestion or not remained unknown.

The amount of TFP production has been steadily increasing in Japan according to the statistics by the Japan Plant Protection Association.[15] There is a strong and urgent need to accumulate human poisoning cases, regardless of whether they are lethal or non-lethal, to spread the awareness and to share the information on this new pesticide and its related chemicals among professionals.

Ethical approval

None declared.

Funding

None declared.

Conflict of interest

The authors have no conflict of interest.

References

1. Food Safety Commission Pesticides. Evaluation report tolfenpyrad. http://www.fsc.go.jp/english/evaluationreports/pesticide/evaluationreport_tolfenpyrad.pdf.
2. National Research Institute of Police Science. *Annual case reports of drugs and toxic poisoning in Japan*; 2005; 2011. p. 47–53 [Japanese].
3. Kudo K, Ishida T, Hikiji W, Usumoto Y, Umehara T, Nagamatsu K, et al. Pattern of poisoning in Japan: selection of drugs and poisons for systematic toxicological analysis. *Forensic Toxicol* 2010;**28**:25–32.
4. Imada Y, Maitani R, Mise M, Hatano Y, Araki H, Endo Y, et al. Acute tebufenpyrad and tolfenpyrad poisoning in humans. *Jpn J Clin Toxicol* 2010;**23**:324–8 [Japanese].
5. Yamaguchi K, Hikiji W, Takino M, Saka K, Hayashida M, Fukunaga T, et al. Analysis of tolfenpyrad and its metabolites in plasma in a tolfenpyrad poisoning case. *J Anal Toxicol* 2012;**36**:529–37.
6. Gunnell D, Eddleston M, Phillips MR, Konradsen F. The global distribution of fatal pesticide self-poisoning: systematic review. *BMC Public Health* 2007;**7**:357.
7. Niitsu H, Fujita Y, Chiba T, Otani M, Yoshioka N, Aoki Y, et al. An autopsy case of fatal poisoning with tebufenpyrad. *Res Prac Med* 2010;**53**:109–13 [Japanese].
8. Kuffner EK. Camphor and moth repellants. In: Goldfrank LR, Flomenbaum NE, Lewin NA, et al., editors. *Goldfrank's toxicologic emergencies*. 7th ed. New York: McGraw-Hill; 2002. p. 1295–302.
9. Lim HC, Poulose V, Tan HH. Acute naphthalene poisoning following the non-accidental ingestion of mothballs. *Singapore Med J* 2009;**50**:e298–301.
10. IRAC Mode of Action Working Group. IRAC Mode of Action Classification (Version 7.2). http://www.irac-online.org/wp-content/uploads/MoA-classification.pdf.
11. Eisinger M, Almog Y. Pyrimidifen intoxication. *Ann Emerg Med* 2003;**42**:289–91.
12. De Wilde A, Heyndrickx A, Carton D. A case of fatal rotenone poisoning in a child. *J Forensic Sci* 1986;**31**:1492–8.
13. Wood D, Alsahaf H, Streete P, Dargan P, Jones A. Fatality after deliberate ingestion of the pesticide rotenone: a case report. *Crit Care* 2005;**9**:280–4.
14. Patel F. Pesticidal suicide: adult fatal rotenone poisoning. *J Forensic Legal Med* 2011;**18**:340–2.
15. Japan Plant Protection Association. *Annual statistics on pests and pesticides (Nouyaku Youran)*. Food Safety and Consumer Affairs Bureau, Ministry of Agriculture, Forestry and Fisheries; 2006–10 [Japanese].